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RESEARCH ARTICLE

Initial BMI effects on clinical presentation and prognosis in neuromyelitis optica spectrum disorder

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Abstract

Objective: To investigate the correlation among body mass index at onset, clinical features, and prognosis in patients with neuromyelitis optica spectrum disorder. **Method**: This retrospective cohort studied patients with neuromyelitis optica spectrum disorder from January 2015 to January 2022, grouping them by body mass index at onset. Demographics and clinical records were reviewed. Anderson–Gill, Kaplan–Meier, and Cox models evaluated the body mass index's effect on relapse risk and long-term outcomes. **Results**: Of 246 patients with 799 neuromyelitis optica spectrum disorder attacks study, 36 patients had low, 133 had normal, 77 had high body mass index, with a mean onset age of 40 ± 13 years, and the population was 88% female. The medium follow-up time was 49 months; AQP4-IgG was found in 193 (78%) patients. Onset and relapse of area postrema syndrome were less frequent in patients with a normal body mass index. The annual relapse rate after immunosuppressive therapy was significantly lower in patients with a low body mass index. In the multivariable analysis, statistical correlation still existed between body mass index at onset and risk of relapse (HR = 1.03, 95% CI: 1.03–1.03, $P < 0.001$), risk of severe attack (HR = 0.92, 95% CI: 0.86–0.98, $P = 0.013$), risk of visual disability (HR = 0.9, 95% CI: 0.81–1, $P = 0.047$), and overall risk of disability (HR = 0.89, 95% CI: 0.82–0.98, $P = 0.015$) after adjusting various variables. **Interpretation**: Lower body mass index at onset was associated with less frequent relapse but poor prognosis.

Introduction

Neuromyelitis optica spectrum disorder (NMOSD) is an inflammatory autoimmune disease that affects the central nervous system (CNS), mainly mediated by the pathogenic autoreactive IgG antibody to aquaporin-4 (AQP4-IgG).[1] NMOSD can be disabling and relapse-dependent, resulting in permanent functional loss.[2] Therefore, it is vital to identify the risk factors for poor outcomes to prevent relapse early in the disease.

Numerous factors have been identified as potential predictors of relapse and permanent disability.[3–5] The link between body mass index (BMI) and several inflammatory and autoimmune diseases has been established.[6–8] More recent studies have suggested a causative relationship between genetic variants associated with BMI and susceptibility to multiple sclerosis[9,10] ([MS], an autoimmune inflammatory demyelinated disease of the CNS), which has also been reported in some observational studies.[11,12]

However, the association between BMI and NMOSD is still a matter of debate, as existing studies have reported contradictory results. A recent study reported an association between lower BMI and poor outcomes in female AQP4-IgG seropositive NMOSD patients,[13] while another study suggested no correlation between NMOSD severity and BMI.[14] Limited by the relatively small sample size, the effect of BMI on the clinical features, disease course, and prognosis of NMOSD has not been adequately studied. Therefore, a large-scale observational study is required to determine the role of BMI in patients with NMOSD. Thus, this study aimed to characterize the nutritional status of

patients with NMOSD and investigate the correlation between BMI at onset and the prognosis of NMOSD.

Methods

Study design and patients

This was a retrospective data analysis from patients prospectively included in the NMOSD cohort at a tertiary medical center in Southwest China (Department of Neurology, West China Hospital, Sichuan University) between January 2015 and January 2022. Patients were included in this study if they met the following criteria: (1) AQP4-IgG seropositive or double seronegative (AQP4-IgG and MOG-IgG) NMOSD diagnosis according to 2015 diagnostic criteria,[15] (2) no use of glucocorticoid (GCs) before BMI measurement, and (3) AQP4-IgG and myelin oligodendrocyte glycoprotein IgG (MOG-IgG) tested. Patients were excluded for the following reasons: (1) with any comorbidity that may affect the measurement of BMI, (2) incomplete data, (3) patients who refused to take immunosuppression therapy (IST), (4) MOG-IgG seropositive, or (5) follow-up time <6 months.

Data collection

The prospective cohort included patients diagnosed with NMOSD during their first visit to our medical center. Demographic information (such as sex, age, and BMI at first onset) and clinical data (including AQP4-IgG and MOG-IgG serology, presentation of onset, Expanded Disability Status Scale [EDSS], and date of initiation of IST) were recorded. All patients were regularly followed up every 6–12 months, a trained neurologist assessed EDSS at each follow-up visit, and details of each relapse event were recorded. Patients who received IST were treated with azathioprine (AZA) at a dose of 100–150 mg/day, or mycophenolate mofetil (MMF) at a dose of 1000–1500 mg/day, depending on disease severity, or rituximab at a dose of (RTX) 375 mg/ m^2 every 6 months.

Outcome measurement

Patients were classified into three groups according to their BMI at onset: those with low BMI (BMI < 18.5 kg/m^2), normal BMI (18.5 $kg/m^2 \leq$ BMI < 24 kg/m^2), and patients with high BMI (BMI $\geq$ 24 kg/m^2), with the cutoff of BMI according to the criteria for weight issued by the Ministry of Health, People's Republic of China.[16] AQP4-IgG and MOG-IgG serologies were detected using a commercial cell-based assay (CBA) (EUROIMMUN AG, Luebeck, Germany).[17,18] Time to relapse, severe attack, and visual and motor disabilities were calculated. Relapse was defined as a new worsening of neurological function lasting more than 24 h without other identifiable causes and occurring more than 30 days after a previous attack.[19] Severe attacks were defined as a visual acuity equal to or worse than 20/200[20–22] or an EDSS over 6.0.[21,23] Permanent visual disability or motor disability was defined as a duration of visual acuity equal to or worse than 20/200 or EDSS over 6.0 for 6 months.[21]

Standard protocol approvals and patient consent

The Ethics Committee of Sichuan University approved this study. Written informed consent was obtained from all the patients.

Statistical analysis

Continuous variables are presented as mean ± SD; these are presented as median (IQR) if they were not normally distributed (Kolmogorov–Smirnov test was applied to verify the normality distribution of continuous variables). Categorical variables are presented as frequency (%). Mean and median differences between the three groups were analyzed using ANOVA or the Kruskal–Wallis test; portions among groups were compared using Fisher's exact test. As this was an exploratory study, multiple comparisons were not conducted.

The risk of a severe attack and visual or motor disabilities was evaluated using Kaplan–Meier curves and Cox proportional hazard regression. The Anderson–Gill (AG) proportional hazard model was used to assess the risk of relapse.[24] A Schoenfeld residual test was performed to evaluate possible violations of the proportional hazard assumption. Age at onset, sex, AQP4-IgG serology, presentation of the first onset, and therapy options were adjusted as covariates. Longitudinal group differences and correlations were analyzed using a linear mixed-effect model, identity of patients and attack type were adjusted as random intercepts. Onset age, sex, and AQP4-IgG serology were controlled for as fixed effects. The onset of the brain stem and cerebral syndromes were combined for analysis (BS) because of their rarity.

All statistical analyses were performed using R; V.3.6.2 (http://www.r-project.org/), survival, and rms packages were used to perform Cox and AG regression. Statistical significance was set at $P < 0.05$.

Results

Study population

Of the 860 patients with NMOSD registered in our medical center from January 2015 to January 2022, 246 met

the inclusion criteria and were included in this study (36 with low BMI, 133 with normal BMI, and 77 with high BMI). The screening process for participants is shown in Figure 1.

Demographic and clinical features

Table 1 summarizes the included patients' demographic and clinical characteristics and outcomes. This cohort was characterized by a mean onset age of 40 ± 13 years, with 88% female population, and a mean BMI of 22.5 ± 3.8 kg/m^2. AQP4-IgG was found in 193 (78%) patients, and the median follow-up time was 49 (28–75) months. Patients with a low BMI had a significantly younger age at onset and a higher proportion of female patients; the AQP4-IgG serology status did not differ among the three groups.

Transverse myelitis (TM) was the most frequent presentation of the first onset (73%), followed by optic neuritis (ON) (56%); the lower ratio of patients who were presented as area postrema syndromes (APS) at onset was found in patients with normal BMI (18/133, $P = 0.021$); only 30 (12%) patients were presented as BS at the first onset.

Disease course and analysis of relapses

All patients received IST as maintenance treatment; the median duration between the onset and initiation of IST was 9 months. Although the interval was longer in patients with high BMI, no statistical significance was observed. During the follow-up period, at least one relapse was recorded in 193 (78%) patients, and a monophasic course was more frequently observed in patients with a low BMI (13/36, 36%). However, no significant difference was found in those with a relapsing course. The interval from onset to the first relapse did not differ among the three groups. Regarding the date of initiation of IST as the cutoff, the annualized relapse rate (ARR) before and after IST was calculated separately. The ARR after IST was significantly higher in patients with high BMI than in patients with low/normal BMI (0.52 vs. 0.33 vs. 0.18, $P = 0.026$), while the ARR before IST and overall ARR were not different among the three groups.

As shown in Table 2, of the 246 patients, 799 NMOSD attacks (onset included) were recorded (92 for patients with low BMI, 424 for patients with normal BMI, and 283 for patients with high BMI). Compared to patients with low or high BMI at onset, patients with normal BMI showed a lower ratio of APS occurrences (18% vs. 6.6% vs. 16%, $P < 0.001$); the highest percentage of multifocal attacks was found in patients with low BMI (23%, $P = 0.009$). Of the 799 episodes, higher severity was observed in patients with a low BMI (median EDSS 3.5 vs. 3 vs. 3, $P = 0.002$).

Long-term prognosis of patients

Eighty-two patients (33%) experienced at least one severe NMOSD attack, while 33 (13%) developed a permanent visual disability, and 17 (6.9%) developed a motor disability; the overall disability rate was 18% (44/246). Long-term outcomes were not significantly different among the three groups.

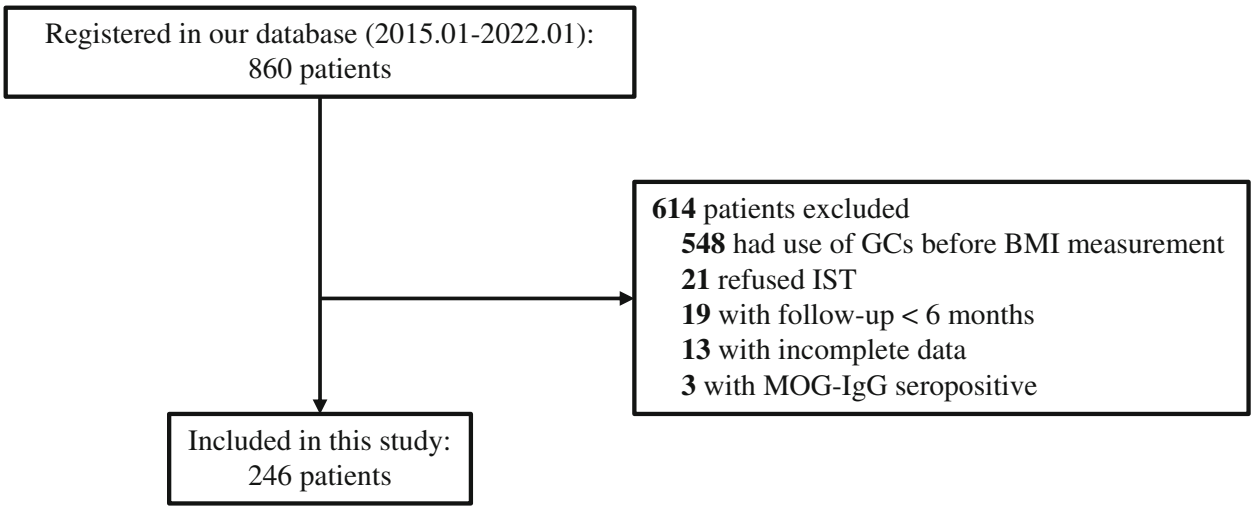

Figure 1. Flowchart for participants screening. BMI, body mass index; GCs, glucocorticoids; IST, immunosuppression therapy; MOG, myelin oligodendrocyte glycoprotein.

Table 1. Demographic and clinical features, and long-term outcome of NMOSD patients according to BMI groups.

Characteristic	Total $N = 246$	Low BMI $N = 36$	Normal BMI $N = 133$	High BMI $N = 77$	*P*-value
Demographic features					
Age at onset	40 (13)	36 (15)	40 (13)	41 (11)	0.083
Sex					
Male	29 (12%)	1 (2.8%)	15 (11%)	13 (17%)	0.082
Female	219 (88%)	35 (97.2%)	118 (89%)	64 (83%)	
BMI at onset	22.5 (3.8)	17.1 (1.0)	21.5 (1.5)	26.9 (2.6)	<0.001
Clinical features					
AQP4-IgG seropositive	193 (78%)	29 (81%)	104 (78%)	60 (78%)	0.954
Type of onset					
ON	137 (56%)	20 (56%)	76 (57%)	41 (53%)	0.862
TM	179 (73%)	25 (69%)	96 (72%)	58 (75%)	0.767
APS	49 (20%)	10 (28%)	18 (14%)	21 (27%)	0.021
BS	30 (12%)	4 (11%)	18 (14%)	8 (10%)	0.861
Disease course					
Duration from onset to IST (months)	9 (3–34)	4 (2–20)	8 (3–31)	17 (3–37)	0.098
Relapsing course	193 (78%)	23 (64%)	106 (80%)	64 (83%)	0.067
Time to first relapse	13 (5–27)	11 (4–28)	14 (5–30)	13 (5–24)	0.697
Overall ARR	0.44 (0.46)	0.41 (0.72)	0.42 (0.39)	0.49 (0.43)	0.073
ARR before IST	0.56 (0.59)	0.59 (0.80)	0.54 (0.58)	0.57 (0.47)	0.6
ARR after IST	0.37 (0.63)	0.18 (0.34)	0.33 (0.48)	0.52 (0.88)	0.026
Disease duration (months)	49 (28–75)	39 (23–62)	48 (28–75)	55 (30–78)	0.145
Outcome					
Severe attack	82 (33%)	16 (44%)	42 (32%)	24 (31%)	0.327
Visual disability	33 (13%)	6 (17%)	19 (14%)	8 (10%)	0.593
Motor disability	17 (6.9%)	3 (8.3%)	9 (6.8%)	5 (6.5%)	0.883
Overall disability	44 (18%)	8 (22%)	26 (20%)	10 (13%)	0.358

Data are presented as *n* (%), mean ± SD, or median (interquartile range). APS, area postrema syndrome; AQP4, aquaporin 4; ARR, annual relapse rate; BMI, body mass index; BS, brain stem/cerebral syndrome; EDSS, Expanded Disability Status Scale; IST, immunosuppression therapy; ON, optic neuritis; TM transverse myelitis.

Table 2. Summarize of NMOSD attacks of patients according to BMI groups.

Characteristic	Total $N = 799$	Low BMI $N = 92$	Normal BMI $N = 424$	High BMI $N = 283$	*P*-value
Presentation of attacks					
ON	245 (31%)	25 (27%)	134 (32%)	86 (30%)	0.705
TM	540 (68%)	66 (72%)	282 (67%)	192 (68%)	0.642
APS	90 (11%)	17 (18%)	28 (6.6%)	45 (16%)	<0.001
BS	86 (11%)	10 (11%)	50 (12%)	26 (9.2%)	0.563
Multifocal	121 (15%)	21 (23%)	50 (12%)	50 (18%)	0.009
EDSS at attacks	3.00 (2.00–4.00)	3.50 (2.00–6.00)	3.00 (2.00–4.00)	3.00 (2.00–4.00)	0.002

Data are presented as *n* (%) or median (IQR). APS, area postrema syndromes; BS, brain stem/cerebral syndromes; EDSS, Expanded Disability Status Scale; ON, optic neuritis; TM, transverse myelitis.

To assess the effect of BMI at onset on the long-term prognosis, we performed a multivariable regression adjusting age at onset, sex, AQP4-IgG serology, treatment status, and presentation of onset; the results are summarized in Tables 3 and 4. The times to first relapse, severe attack, and visual and motor disabilities are shown in Figure 2. No significant differences in long-term outcomes were observed among the three groups. In the AG model, BMI at onset predicted the risk of relapse: every additional 1 kg/m^2 at onset increased the risk of relapse by

Table 3. The effect of BMI at onset on the risk of relapses with multivariable Anderson–Gill proportional hazards model.

Variables	HR	CI 95%	*P* value
BMI at onset (per 1 kg/m^2)	1.03	1.03–1.03	<0.001
Age at onset (per year)	1.01	1.01–1.01	<0.001
Sex			
Female	1 (Ref.)	–	–
Male	0.96	0.94–0.99	0.005
AQP4-IgG serology			
AQP4-IgG seronegative	1 (Ref.)	–	–
AQP4-IgG seropositive	0.8	0.78–0.81	<0.001
Treatment status			
IST	1 (Ref.)	–	–
NT	2.95	2.89–3.01	<0.001
Presentation of onset			
ON onset	0.72	0.71–0.74	<0.001
TM onset	1.07	1.05–1.1	<0.001
APS onset	1.38	1.35–1.41	<0.001
BS onset	1.44	1.4–1.49	<0.001

Adjusted for onset age, sex, AQP4-IgG serology, treatment status and presentation of onset. APS, area postrema syndromes; AQP4, aquaporin 4; BS, brain stem/cerebral syndromes; IST, immunosuppression therapy; NT, no therapy; ON, optic neuritis; TM, transverse myelitis.

Table 4. Multivariable cox proportional regression for the effect of BMI at onset on the prognosis of NMOSD patients.

	BMI (per 1 kg/m^2)		
	HR	CI 95%	*P* value
Risk for the first relapse	1.01	0.97–1.05	0.613
Risk for severe attack	0.92	0.86–0.98	0.013
Risk for visual disability	0.9	0.81–1	0.047
Risk for motor disability	0.92	0.79–1.07	0.267
Overall risk for disability	0.89	0.82–0.98	0.015

Adjusted for onset age, sex, AQP4-IgG serology, and presentation of onset. BMI, body mass index.

3% ($P < 0.001$). In the Cox proportional hazard regression, BMI at onset was not associated with the risk for the first relapse and risk for motor disability; while BMI at onset was a protective factor for severe attack and visual disability; every additional 1 kg/m^2 at onset decreased the risk of severe attack by 8% (95% CI: 0.86–0.98, $P = 0.013$), reduced the risk of visual disability by 10% (95% CI: 0.81–1, $P = 0.047$), and decreased the overall risk of disability by 11% (95% CI: 0.82–0.98, $P = 0.015$).

Figure 3 shows the longitudinal changes in EDSS scores in the three BMI groups. Patients with a low BMI showed higher EDSS scores throughout the disease duration. However, a rapid increase in EDSS over NMOSD relapse was observed in patients with a high BMI (B = 0.23, SE = 0.10, $P = 0.039$).

Discussion

Obesity is associated with an increased risk for various autoimmune diseases.[25] However, studies on the effects of obesity on NMOSD have shown different results.[13,14,25] Baek et al.[13] reported that a low BMI was a risk factor for poor outcomes in female NMOSD patients. Paz et al.[14] did not find an effect of excess weight in patients with NMOSD in their case–control study, but a relatively small sample size (26 pairs) may have limited the power of the analysis. Wu et al. performed a cohort study to investigate the effect of triglycerides (TG) in NMOSD, in which BMI was only adjusted as a covariate,[25] and no effect of BMI in patients with NMOSD was reported. In the present cohort, we compared the demographic and clinical features in different BMI groups and analyzed the impact of BMI on the long-term outcome of patients with NMOSD. We found that lower BMI at onset was associated with less frequent relapse but poor prognosis. Our research supports the former studies and provides a deeper understanding of this issue.

A previous systematic review suggested that corticosteroids may result in a significant gain of body weight, and intravenous methylprednisolone (IVMP) is widely administered in patients with an acute attack. To eliminate the effect of corticosteroid use, patients who received any corticosteroid before the body weight was recorded were all excluded. We regarded 24 kg/m^2 as the cutoff BMI according to the Chinese Ministry of Health's Chinese criteria, which is more appropriate for estimating the nutritional status of the Chinese population than the WHO criteria. According to previous studies, sex and AQP4-IgG seropositivity are risk factors for the prognosis of NMOSD. Our previous study also revealed that therapy options were related to different outcome[19]; therefore, these factors were adjusted as covariates in the multivariable regression.

Numerous studies have revealed the relationship between obesity and autoimmune diseases. Obesity has been found to increase the risk of conditions such as MS, rheumatoid arthritis, systemic lupus erythematosus, and inflammatory bowel disease and decrease treatment efficacy.[26–30] In this study, we confirmed the influence of BMI at onset on the disease activity of NMOSD patients; compared to patients with low/normal BMI, patients with high BMI at onset tended to have more frequent relapses ($P = 0.074$). The analysis of ARR before and after IST initiation showed different results; ARR before IST did not differ among the three groups, while patients with higher BMI at onset showed higher ARR after IST compared to patients with low/normal BMI, indicating a compromised response to IST in patients with high BMI. In the AG regression model, after adjusting for maintenance

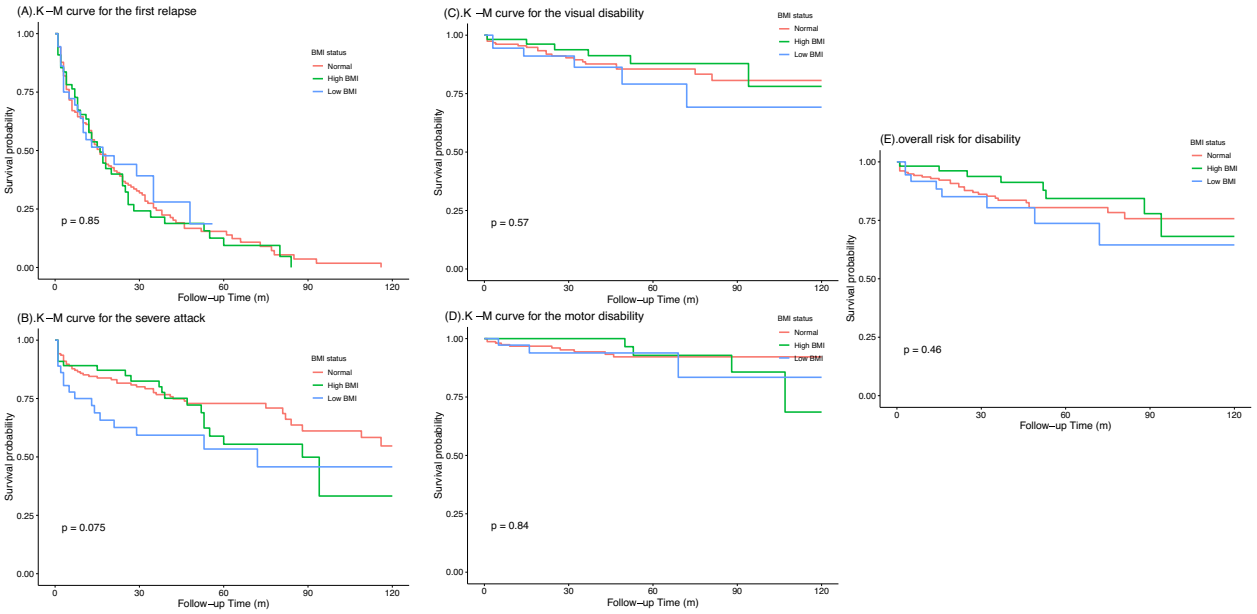

Figure 2. Kaplan–Meier curves for time to the first relapse, severe attack, visual and motor disability. (a) Time to the first relapse was not different among the three groups, (b) time to severe attack was not different among the three groups, (c) time to visual disability was not different among the three groups, (d) time to motor disability was not different among the three groups. (e) Overall risk of disability was not different among the three groups.

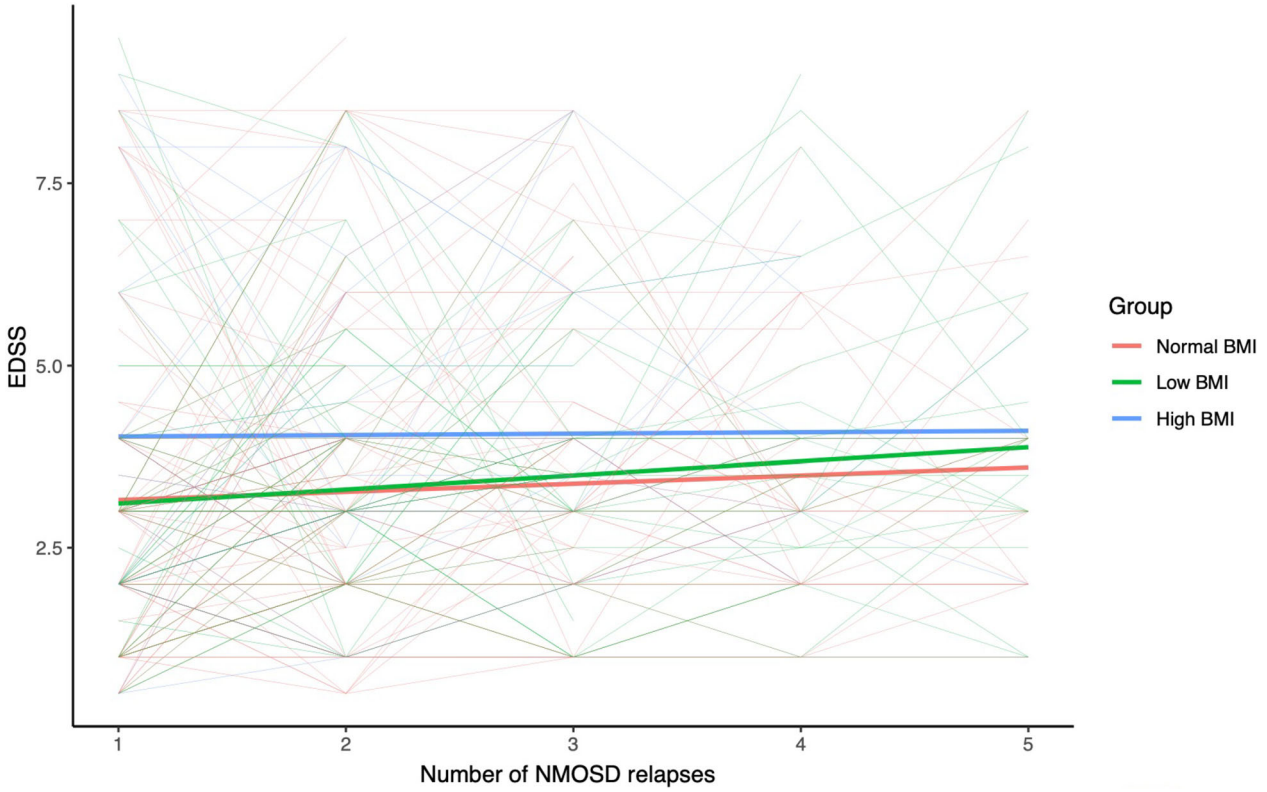

Figure 3. Plots of longitudinal change in EDSS over relapses. The thinner lines show individual-based values and thicker lines show fitted linear mixed-effect models.

treatment status at each relapse, a positive association was found between BMI at onset and the risk of relapse. Our study suggests that BMI at onset affects the risk of relapse, which was probably mediated by the effect of BMI on the efficacy of immunosuppressive therapy. Cellular and molecular data in other diseases demonstrated that obesity resulted in macrophage activation, an increase of Th17, TNF-α, and decreased Treg.[31–33] These changes were also a significant factor in the pathogenesis in NMOSD,[34–39] which can account for the heightened disease activity observed in patients with higher BMI. To validate our results, more research is needed to examine alterations in the phenotype and function of immune cells, along with corresponding cytokines, in NMOSD patients with varying BMI levels.

Baek et al. reported that a lower BMI was a risk factor for poor outcomes in female NMOSD patients with AQP4-IgG seropositive.[13] Patients with AQP4-IgG seropositivity and AQP4-IgG/MOG-IgG double-negativity were included in our cohort. Although the prognosis was not different among the three groups, patients with low BMI still showed poor outcomes compared to those with high BMI in Kaplan–Meier curves. After adjusting for serological status and sex, we found an association between lower BMI and poor prognosis in regression models. Patients with low BMI showed a higher risk of severe attacks and a higher EDSS at each episode, indicating that the poor prognosis of patients with low BMI was more strongly associated with the severity than the frequency of attacks. However, the BMI at onset was not associated with the risk of motor disability, which may be due to the rarity of the events (only 17 patients developed motor disability).

Although the risk of relapse was lower in patients with low BMI, these patients had a higher risk of severe attack and finally developed a permanent disability. Thus, neurologists should consider the severe consequence for patients with low BMI. Risk monitoring and early initiation of IST and rehabilitation are necessary for preventing poor prognosis. However, this study suggested that patients with higher BMI had a higher relapse risk. Therefore, neurologists should notice the effect of BMI on relapse risk in clinical practice. Additionally, monitoring BMI and disease activity might help recognize patients with high relapse risk. Thus, patients should be actively managed to prevent relapses.

Furthermore, studies have revealed weight bias in the medical field. Obese patients were less respected by healthcare providers, resulting in less effective communication.[40,41] Obese patients may sense these attitudes and avoid follow-up and preventive care.[42] Thus, physicians should be aware of this concern and weight bias should be avoided in medical practice.

Our study has several limitations. First, we used BMI to evaluate nutritional status; however, many studies have shown that the association between BMI and the percentage of body fat differs across age and sex,[43] which could have resulted in a biased estimation of overweight status, although we adjusted those factors as covariates in the regression models. Second, owing to our cohort's relatively small sample size, we could not perform subgroup analysis across different strata. Third, patients with double negative serology were not excluded, which limits the interpretability of our study given the different disease courses of AQP4-IgG seropositive and AQP4-IgG seronegative NMOSD. Finally, we only evaluated the effect of BMI at onset while BMI varies over time. This is a retrospective observation study, and further prospective longitudinal cohort studies are needed to explore the effect of BMI on NMOSD prognosis and their causal relationship.

In conclusion, our study showed that a low BMI was associated with a higher risk of permanent disability and higher treatment efficacy but a lower risk of relapse in NMOSD patients. These findings suggested that BMI at onset could be valuable in identifying high-risk patients and could predict the outcome. However, in the present study, the predictive value of BMI is limited because only BMI at the first attack was obtained. Therefore, prospective cohort studies are required to evaluate the effects of dynamic BMI on disease course and prognosis in patients with NMOSD.

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Author Contributions

Wenqin Luo: study design and manuscript writing. Ziyan Shi and Xiaofei Wang: study design and data collection. Hongxi Chen and Lingyao Kong: data collection. Hongyu Zhou: study design and statistical analysis.

Conflict of Interest

The authors declare that they have no competing interests. No disclosure relevant to the manuscript.

References

1. Graber DJ, Levy M, Kerr D, Wade WF. Neuromyelitis optica pathogenesis and aquaporin 4. J Neuroinflammation. 2008;5:22. doi:10.1186/1742-2094-5-22
2. Jarius S, Paul F, Weinshenker BG, Levy M, Kim HJ, Wildemann B. Neuromyelitis optica. Nat Rev Dis Primers. 2020;6(1):85. doi:10.1038/s41572-020-0214-9
3. Mealy MA, Mossburg SE, Kim SH, et al. Long-term disability in neuromyelitis optica spectrum disorder with a history of myelitis is associated with age at onset, delay in diagnosis/preventive treatment, MRI lesion length and presence of symptomatic brain lesions. Mult Scler Relat Disord. 2019;28:64-68. doi:10.1016/j.msard.2018.12.011
4. Sepulveda M, Delgado-Garcia G, Blanco Y, et al. Late-onset neuromyelitis optica spectrum disorder. Neurol Neuroimmunol Neuroinflamm 2019;6(6):e607. 10.1212/NXI.0000000000000607.
5. Palace J, Lin DY, Zeng DL, et al. Outcome prediction models in AQP4-IgG positive neuromyelitis optica spectrum disorders. Brain. 2019;142:1310-1323. doi:10.1093/brain/awz054
6. Harpsoe MC, Basit S, Andersson M, et al. Body mass index and risk of autoimmune diseases: a study within the Danish National Birth Cohort. Int J Epidemiol. 2014;43(3):843-855. doi:10.1093/ije/dyu045
7. Peng HX, Wu XR, Wen YK, Lin JS. Association between elevated body mass index in non-smokers and autoimmune diseases: a two-sample Mendelian randomization analysis. Autoimmun Rev. 2021;20(7):102853. doi:10.1016/j.autrev.2021.102853
8. Klaasen R, Wijbrandts CA, Gerlag DM, Tak PP. Body mass index and clinical response to infliximab in rheumatoid arthritis. Arthritis Rheum. 2011;63(2):359-364. doi:10.1002/art.30136
9. Gianfrancesco MA, Glymour MM, Walter S, et al. Causal effect of genetic variants associated with body mass index on multiple sclerosis susceptibility. Am J Epidemiol. 2017;185(3):162-171. doi:10.1093/aje/kww120
10. Mokry LE, Ross S, Timpson NJ, Sawcer S, Davey Smith G, Richards JB. Obesity and multiple sclerosis: a Mendelian randomization study. PLoS Med. 2016;13(6):e1002053. doi:10.1371/journal.pmed.1002053
11. Munger KL, Chitnis T, Ascherio A. Body size and risk of MS in two cohorts of US women. Neurology. 2009;73(19):1543-1550. doi:10.1212/WNL.0b013e3181c0d6e0
12. Hedström AK, Olsson T, Alfredsson L. High body mass index before age 20 is associated with increased risk for multiple sclerosis in both men and women. Mult Scler. 2012;18(9):1334-1336. doi:10.1177/1352458512436596
13. Baek SH, Kim JS, Jang MJ, et al. Low body mass index can be associated with the risk and poor outcomes of neuromyelitis optica with aquaporin-4 immunoglobulin G in women. J Neurol Neurosurg Psychiatry. 2018;89(11):1228-1230. doi:10.1136/jnnp-2017-317202
14. Paz ÉS, Maciel P, D'Almeida JAC, et al. Excess weight, central adiposity and pro-inflammatory diet consumption in patients with neuromyelitis optica spectrum disorder. Mult Scler Relat Disord. 2021;54:103110. doi:10.1016/j.msard.2021.103110
15. Wingerchuk DM, Banwell B, Bennett JL, et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. Neurology. 2015;85(2):177-189. doi:10.1212/wnl.0000000000001729
16. China N. Criteria of weight for adults (WS/T 428–2013). Standards Press of China; 2013.
17. Jarius S, Probst C, Borowski K, et al. Standardized method for the detection of antibodies to aquaporin-4 based on a highly sensitive immunofluorescence assay employing recombinant target antigen. J Neurol Sci. 2010;291(1–2):52-56. doi:10.1016/j.jns.2010.01.002
18. Mariotto S, Ferrari S, Gastaldi M, et al. Neurofilament light chain serum levels reflect disease severity in MOG-Ab associated disorders. J Neurol Neurosurg Psychiatry. 2019;90(11):1293-1296. doi:10.1136/jnnp-2018-320287
19. Shi Z, Du Q, Chen H, et al. Effects of immunotherapies and prognostic predictors in neuromyelitis optica spectrum disorder: a prospective cohort study. J Neurol. 2020;267(4):913-924. doi:10.1007/s00415-019-09649-7
20. Songthammawat T, Srisupa-Olan T, Siritho S, et al. A pilot study comparing treatments for severe attacks of neuromyelitis optica spectrum disorders: intravenous methylprednisolone (IVMP) with add-on plasma exchange (PLEX) versus simultaneous ivmp and PLEX. Mult Scler Relat Disord. 2020;38:101506. doi:10.1016/j.msard.2019.101506
21. Camera V, Messina S, Elhadd KT, et al. Early predictors of disability of paediatric-onset AQP4-IgG-seropositive neuromyelitis optica spectrum disorders. J Neurol Neurosurg Psychiatry. 2022;93(1):101-111. doi:10.1136/jnnp-2021-327206
22. Lange C, Feltgen N, Junker B, Schulze-Bonsel K, Bach M. Resolving the clinical acuity categories "hand motion" and "counting fingers" using the Freiburg Visual Acuity Test (FrACT). Graefes Arch Clin Exp Ophthalmol. 2009;247(1):137-142. doi:10.1007/s00417-008-0926-0
23. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology. 1983;33(11):1444-1452. doi:10.1212/wnl.33.11.1444
24. Amorim LD, Cai J. Modelling recurrent events: a tutorial for analysis in epidemiology. Int J Epidemiol. 2015;44(1):324-333. doi:10.1093/ije/dyu222
25. Wu K, Wen L, Duan R, et al. Triglyceride level is an independent risk factor in first-attacked neuromyelitis optica spectrum disorders patients. Front Neurol. 2019;10:1230. doi:10.3389/fneur.2019.01230

26. Hedstrom AK, Bomfim IL, Barcellos L, et al. Interaction between adolescent obesity and HLA risk genes in the etiology of multiple sclerosis. Neurology. 2014;82(10):865-872. doi:10.1212/wnl.0000000000000203
27. Chaiamnuay S, Bertoli AM, Fernandez M, et al. The impact of increased body mass index on systemic lupus erythematosus – data from LUMINA, a multiethnic cohort. J Clin Rheumatol. 2007;13(3):128-133. doi:10.1097/RHU.0b013e3180645865
28. Katz P, Yazdany J, Julian L, et al. Impact of obesity on functioning among women with systemic lupus erythematosus. Arthritis Care Res. 2011;63(10):1357-1364. doi:10.1002/acr.20526
29. Lu B, Hiraki LT, Sparks JA, et al. Being overweight or obese and risk of developing rheumatoid arthritis among women: a prospective cohort study. Ann Rheum Dis. 2014;73(11):1914-1922. doi:10.1136/annrheumdis-2014-205459
30. Crowson CS, Matteson EL, Davis JM 3rd, Gabriel SE. Contribution of obesity to the rise in incidence of rheumatoid arthritis. Arthritis Care Res (Hoboken). 2013;65(1):71-77. doi:10.1002/acr.21660
31. Wang S, Baidoo SE, Liu Y, et al. T cell-derived leptin contributes to increased frequency of T helper type 17 cells in female patients with Hashimoto's thyroiditis. Clin Exp Immunol. 2013;171(1):63-68. doi:10.1111/j.1365-2249.2012.04670.x
32. Mikita J, Dubourdieu-Cassagno N, Deloire MS, et al. Altered M1/M2 activation patterns of monocytes in severe relapsing experimental rat model of multiple sclerosis. Amelioration of clinical status by M2 activated monocyte administration. Mult Scler. 2011;17(1):2-15. doi:10.1177/1352458510379243
33. Emamgholipour S, Eshaghi SM, Hossein-nezhad A, Mirzaei K, Maghbooli Z, Sahraian MA. Adipocytokine profile, cytokine levels and foxp3 expression in multiple sclerosis: a possible link to susceptibility and clinical course of disease. PLoS One. 2013;8(10):e76555. doi:10.1371/journal.pone.0076555
34. Ma X, Qin C, Chen M, et al. Regulatory T cells protect against brain damage by alleviating inflammatory response in neuromyelitis optica spectrum disorder. J Neuroinflammation. 2021;18(1):201. doi:10.1186/s12974-021-02266-0
35. Cho EB, Cho HJ, Seok JM, Min JH, Kang ES, Kim BJ. The IL-10-producing regulatory B cells (B10 cells) and regulatory T cell subsets in neuromyelitis optica spectrum disorder. Neurol Sci. 2018;39(3):543-549. doi:10.1007/s10072-018-3248-y
36. Ikeguchi R, Shimizu Y, Suzuki S, et al. Japanese cases of neuromyelitis optica spectrum disorder associated with myasthenia gravis and a review of the literature. Clin Neurol Neurosurg. 2014;125:217-221. doi:10.1016/j.clineuro.2014.07.036
37. Barros PO, Dias ASO, Kasahara TM, et al. Expansion of IL-6(+) Th17-like cells expressing TLRs correlates with microbial translocation and neurological disabilities in NMOSD patients. J Neuroimmunol. 2017;307:82-90. doi:10.1016/j.jneuroim.2017.04.001
38. Lin J, Li X, Xia JX. Th17 cells in neuromyelitis optica spectrum disorder: a review. Int J Neurosci. 2016;126(12):1051-1060. doi:10.3109/00207454.2016.1163550
39. Hou MM, Li YF, He LL, et al. Proportions of Th17 cells and Th17-related cytokines in neuromyelitis optica spectrum disorders patients: a meta-analysis. Int Immunopharmacol. 2019;75:75105793. doi:10.1016/j.intimp.2019.105793
40. Phelan SM, Dovidio JF, Puhl RM, et al. Implicit and explicit weight bias in a national sample of 4,732 medical students: the medical student CHANGES study. Obesity (Silver Spring). 2014;22(4):1201-1208. doi:10.1002/oby.20687
41. Huizinga MM, Cooper LA, Bleich SN, Clark JM, Beach MC. Physician respect for patients with obesity. J Gen Intern Med. 2009;24(11):1236-1239. doi:10.1007/s11606-009-1104-8
42. Cohen SS, Palmieri RT, Nyante SJ, et al. Obesity and screening for breast, cervical, and colorectal cancer in women: a review. Cancer. 2008;112(9):1892-1904. doi:10.1002/cncr.23408
43. WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet. 2004;363(9403):157-163. doi:10.1016/S0140-6736(03)15268-3

